“ SYNTHESIS AND CHARACTERIZATION OF NEW PYRIMIDINE DERIVATIVES AND SCREENING OF THEIR PHARMACOLOGICAL PROPERTIES”

SHORT RESUME OF THE PLAN PROPOSED FOR INVESTIGATION FOR Ph.D. DEGREE UNDER THE FACULTY OF SCIENCE.

To be submitted to

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"Synthesis and Characterization of New Pyrimidine Derivatives and Screening of Their Pharmacological Properties"

1. Introduction:

Heterocyclic compounds and their derivatives have been widely used in agronomy and medicine because of their unique biological activity, which is used in many biological fields, due to it is an activity in multiple illnesses. Biological molecules such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many more contains the heterocyclic ring in the major skeleton. There are a lot of heterocyclic compounds which have applications in many common diseases such as; triazine derivatives have been used as antimicrobial herbicides, urinary antiseptics, and anti-inflammatory agents. Benzimidazole derivatives have been reported to possess a wide range of biological activities such as antibacterial, antifungal, antiviral, and anthelmintic, etc.

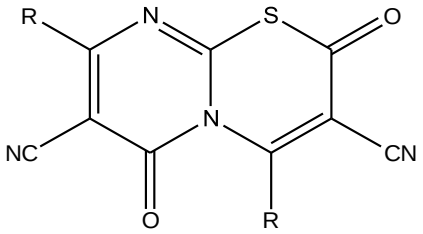
Ketene Dithio acetals are attractive building blocks for the synthesis of heterocyclic compounds. In particular, pyrimidine derivatives have been the subject of chemical and biological studies due to their interesting pharmacological activity, including antipyretic, analgesic, anti-inflammatory potential as well as herbicide, fungicide, and elephanticides properties. This work aimed to synthesize some pyrimidine derivatives with the hope of obtaining interesting biological activities.

They also find applications as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, and dyestuff. They have been applied to fluorescence chemo sensors and can be used as organic light-emitting devices.

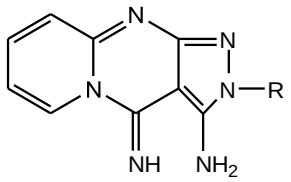
2. Review of Literature and Development in the subject (Previous work done in the relevant area):

Now we are working on the development of the Nitrogen, Sulphur containing fused heterocyclic compounds by applying different catalytic reagents. Some of them have been mentioned below. The present work with our research group involves the synthesis of novel biological active fused heterocycles containing imino /oxo pyrimdine ring fused through the nitrogen atom with another biologically active nucleus such as Pyridine, Imidazole pyrazole, thiazole, benzothiazole, and quinolines which are published in different reputed journals.

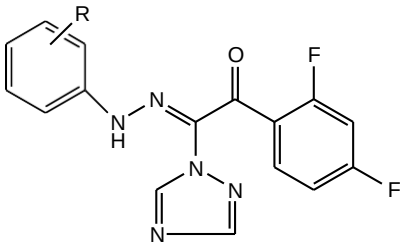
- Simple and efficient synthesis of substituted pyrimido [2,1-*b*][1,3] thiazines, Sambhaji P. Vartale et.al[1] ***Heterocyclic Communication*** 2013,19(3), 215-218.



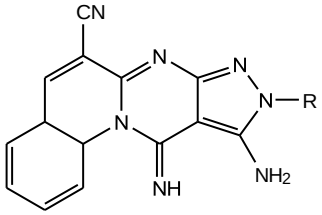
- An efficient synthesis of some novel 3-cyano-4-imino-2-(methylthio)-4H-pyrido[1,2- *a*] pyrimidine and their derivatives, Sambhaji P. Vartale, et al.[2] ***J. Heterocyclic Chem,*** 2013, 50, 351-355.



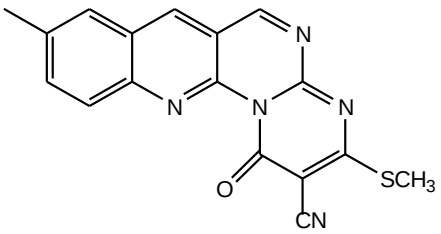
- Synthesis and biological activity of some fluorinated arylhydrazotriazoles, M.S.Shingare, S.A.Sadaphal et. al.[3] ***Arabian Journal of Chemistry***, 2012, 5, 257-261.



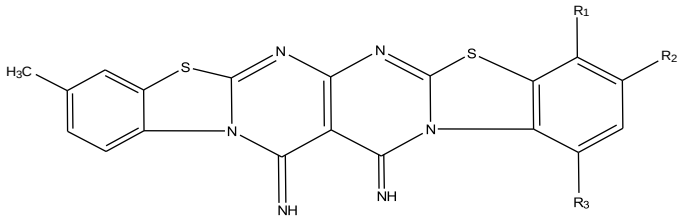
- Synthesis and Antimicrobial Evaluation of 3-amino-11- cyano-4-iminopyrazolo [4, 5-*e*]-4H-pyrimido [2,1-*b*] quinoline and their substituted derivatives. Sambhaji P.Vartale et al.[4] ***Heteroletter***, 2012,2, (1),71-78.



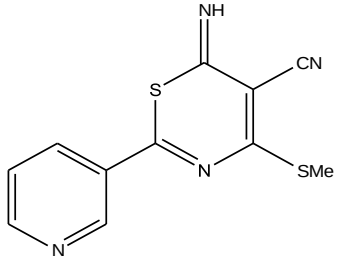
- Convenient one pot synthesis of 3-cyano-9-methylthio-4-oxo-4H-pyrimido[2,1-*b*] quinoline and its reactions with selected nucleophiles, Sambhaji P. Vartale et al.[5] ***Letters in Organic Chemistry***, 2009, 6(7), 544-548.



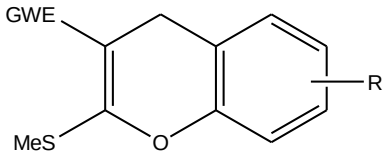
- A Convenient one pot synthesis and antimicrobial activity of 10-methyl-14,15-diimino benzothiazolo[2,3-*b*]pyrimido [5,6-*e*] pyrimido [2,3-*b*]benzothiazole and their substituted derivatives Sambhaji P.Vartale and Sharad V. Kuberkar et al[6] **Journals of *Pelagia Research Library***, 2011, 2(6), 46-51.



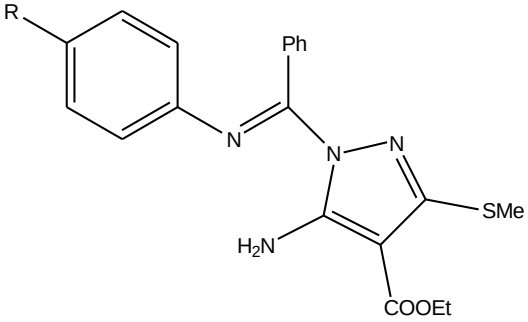
- Synthesis and antioxidant activity of 6-imino-4-(methylthio)-2-(pyridine-3-yl)-6H-1,3-thiazine-5-carbonitrile, Sambhaji P. Vartale et. al[7], **Journals of *International Research Journal of Pharmacy***, DOI: 10.7897/2230-8407.089172.



- One-Pot Synthesis of Polyfunctionalized 4H-Chromenes and Dihydrocoumarins Based on Copper (II) Bromide-Catalyzed CC Coupling of Benzylic Alcohols with Ketene Dithioacetals4, Qun Liu et.al, ***Adv. Synth. Catal.*** 2010, 352, 1593 – 1599.



- Reaction of ethyl 2-cyano-3,3- bis(methylthio)acrylate with amidrazones; synthesis of new mercapto pyrazoles and NMR investigation, A.A. Aly, et.al. Journal of Sulfur Chemistry, 2015, Vol.36,2015, issue-5



3. Objectives of Research/ Proposed Hypothesis:

- Design synthesis of novel catalytic reagents.
- Extending the research of novel catalytic reagents to new domains, especially targeting the synthesis of different novel imino/oxo fused heterocyclic derivatives.
- Studying mechanistic details and pathways of novel catalytic reagents.
- Investigate the role of novel catalytic reagents in the activation of substances.
- Establishment of the structure of newly synthesized compounds with help of spectral data.
- Evaluation of physicochemical properties of synthesized novel imino/oxo fused heterocyclic compounds
- Evaluation of biological properties of synthesized novel imino/oxo fused heterocyclic compounds.
- Studying Molecular modeling of synthesized compounds.

4. Methodology to be adopted:

- Literature Survey.
- Synthesis and conformation of the structure of catalytic reagents.
- Synthesis and characterization of different imino/oxo fused heterocyclic derivatives by applying novel catalytic reagents.
- Characterization of newly synthesized heterocyclic compounds such as XRD, IR, ^{1}H-NMR, ^{13}C-NMR, Mass Spectroscopy.
- Study of the physicochemical parameter of synthesized compounds.
- Evaluation of microbiological activities of synthesized compounds.
- Submission of data to International /National reputed journals for publication.

5. Importance of study/ Society application:

- **International Status:**

Due to the great interest in this class of pharmacologically active compounds, we report the preparation of novel functionalized azolopyrimidine derivatives by the reaction of ketene S,S-acetal derivatives and with some aminoazoles in the presence (or absence) of triethylamine. These compounds show fluorescence properties and can be used as OLEDs. and It also helps in preventing many viral, fungal and bacterial disease as well as they act as anti-tuberculosis and antioxidant drug with low toxicity. Because of the high efficiency of these compounds following research groups have recognized the importance of this field and made substantial contribution internationally.

1. **Yoshinori Tominaga**
   Faculty of Environmental Studies,
   1-14, Bunkyo-machi,
   Nagasaki 852-8521, Japan.

2. **M.A.Metwally**
   Department of Chemistry,
   Faculty of Science,
   Mansoura University,
   Mansoura, Egypt.

3. **W.Ried**
   Institute of Organic Chemistry,
   University of Frankfurt Laboratory Niederrad.
   Theodor-Stern-Kai 7. o-6000 Frankfurt am Main 70,
   West Germany.

- **National Status:**

Nitrogen, Sulphur, and oxygen-containing heterocycles such as pyrimidine, pyrazole, imidazole, quinoline benzothiazole, and Pyrazole have been widely used in drug molecules these compounds act as antiviral, antifungal, anti-HIV, anticancer, antioxidant, anti-inflammatory agents with low toxicity. Because of the high efficiency of these compounds, the following research groups have recognized the importance of this field and made significant contributions nationally.

1. **Dr. A. T. Bigu**
   Organic Chemistry Division,
   National Chemical Laboratory,
   Pune, India.

2. **Dr. N. T. Patil**
   Organic Chemistry Division II,
   Indian Institute of Chemical Technology,
   Hyderabad-500 007, India.

3. **Dr. D. S. Reddy**
   Organic Chemistry Division,
   National Chemical Laboratory,
   Pune, India.

- **Significance of the study:**

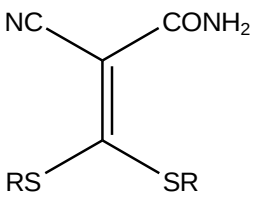
The investigation of novel antimicrobial drugs is an area characterized by vigorous exploration with the goal of overcoming the occurrence of multiple drug resistance. Fused heterocyclic rings like pyridine, pyrimidine, quinoline, thiazole, pyrazole, and benzothiazole, were found to be biologically active compounds.

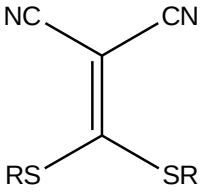
A fused heteroaromatic group containing sulfur, nitrogen, oxygen, etc atoms plays an important role as the heteroaromatic is incorporated into the structure of many pharmaceuticals.

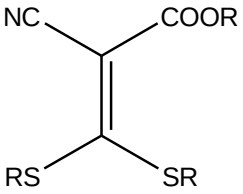
5. Proposed work plan/ Formulation and structure of study:

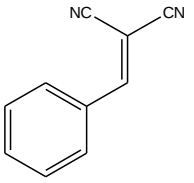
a) Synthesis of amino heterocycles and reagents: (Ist Year)

In the proposed research work we plan to synthesize different ketene dithioacetals and different substituted amino heterocycles containing sulfur, nitrogen, and oxygen as heteroatom.

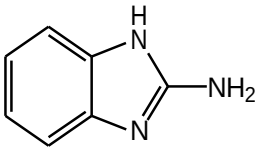




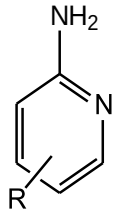




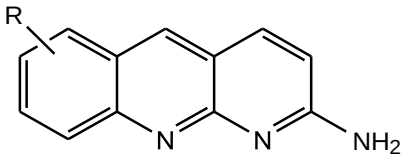
2-benzylidenemalononitrile



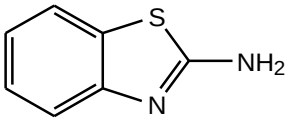
Substituted 2-Amino Benzimidazole



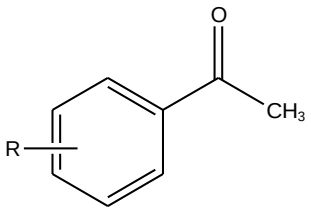
Substituted 2-amino pyridine

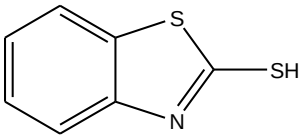


Substituted benzoquinolin-2-amine



Substituted 2-amino benzothiazole





b) Condensation of synthesized amino heterocycles with different reagents: (IInd year)

The synthesized amino heterocycles which contain more than one hetero atom as hetero atom condensation with reagents like guanidine hydrochloride, thiourea, and urea to synthesize main heterocyclic compounds.

Synthesized parent compounds treated with different substituted aniline, phenol, Heterylamine, and active methylene compounds will give new heterocyclic derivatives.

The above new parent pyrimido compound was condensed with a compound containing nitrogen atoms like hydrazine hydrate, Hydrazeno heterocycles, and carbonyl compounds to obtain new fused pyrazolo series derivatives.

Purification of synthesized compounds by using crystallization and conformation of the structure by using spectral data.

c) Evaluation of Physicochemical Parameters: (IIIrd Year)

The physicochemical study of heterocyclic compounds has a very wide scope as this study can demonstrate how our synthesized compounds affect physical properties such as solubility, density, viscosity, and refractive index. Study of Molecular modeling of the newly synthesized compound. Molecular modeling is **an efficient way of studying protein-protein interactions**. It provides detailed information about how protein residues interact with each other at the atomic level. Molecular docking is **a technique that predicts the preferred orientation, affinity, and interaction of a ligand in the binding site of a protein**.

d) Evaluation of Biological Activity: (IIIrd Year)

The above newly synthesized compounds are to be screened for their pharmacological properties like antioxidant, antimicrobial, antimalarial, antifungal, antituberculosis, anticancer, anti-inflammatory, etc.

Hence, the present research work aimed to **"Synthesis and Characterization of New Pyrimidine Derivatives and Screening of Their Pharmacological Properties"**

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